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Molecular Epidemiology of Adenovirus Types 3 and 7 Isolated From Children With Pneumonia in Beijing

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One hundred fifty strains of adenovirus serotypes 3 (Ad3) and 7 (Ad7) were analyzed. The viruses were isolated from patients, the majority of whom had pneumonia, from central and suburban Beijing over a 33-year period (1958–1990). Genomic analysis of DNA extracted from 74 strains of Ad3 and 76 strains of Ad7, with four to five restriction endonucleases (REs), revealed the presence of four and eight genome types, respectively: Ad3a2, Ad3a4, Ad3a5, Ad3a6 and Ad7p1, Ad7a1, Ad7a4, Ad7b, Ad7b1, Ad7d, Ad7d1, and Ad7g. Ad7b1 was the most recently identified genome type. The restriction patterns obtained from 19 representatives of Ad7 genome types after cleavage of the DNA with 12 REs are shown. Ad3a2 first appeared in 1962, and predominated from 1983 to 1988. Ad3a4 was the main causative agent of pneumonia in 1982. Ad3a2 and Ad3a4 are closely related and have 97% pairwise comigrating restriction fragments (PCRF). Ad7d predominated over a period of 11 years (1980–1990). It has 98% PCRF with Ad7b. Ten pairs of strains isolated from different specimens of the same patients were all concordant.

KEY WORDS: restriction pattern, genome type identification, nomenclature system

INTRODUCTION

To date, 49 adenovirus serotypes have been recognised [Russell et al., 1995; Schnurr and Dondero 1993]. Adenovirus serotypes 3 (Ad3) and 7 (Ad7) are two of the most common causative agents of acute respiratory infections and ocular diseases throughout the world, especially in children and military recruits. These diseases include pneumonia, pharyngoconjunctival fever, and conjunctivitis [Huebner et al., 1954; Teng 1960; Kawana et al., 1966; Dudding et al., 1972; Germanis and Jeansson, 1973; Similä et al., 1981; Hong et al., 1986].

Since 1978, there has been considerable world-wide interest in the use of restriction endonucleases (REs) to investigate the genomic variability of the Ad3 and Ad7 genome types (GTs) and to evaluate their relative virulence [Wadell et al., 1985; Wadell, 1984; Wadell and Varsanyi, 1978; Bailey and Richmond, 1986; O'Donnell et al., 1986; Arens and Worth, 1988; Guo et al., 1988; Kannemeyer et al., 1988; Adrian et al., 1989; Itakura et al., 1990; Golovina et al., 1991; Kajon and Wadell, 1994]. Using 12 REs, 17 GTs of Ad3 and 15 GTs of Ad7 have been identified [Li and Wadell 1986, 1988].

The extent of the involvement of adenoviruses in lower respiratory tract disease has not been studied thoroughly by RE analysis in many countries. However, RE analysis of 212 strains isolated in Chile, Uruguay, and Argentina, identified 179 isolates as genome type Ad7h. The genome type Ad7h was found to predominate in these countries over a 5-year period (1986–1990) [Kajon and Wadell, 1994].

In the present study of the molecular epidemiology of adenovirus associated with pneumonia in Beijing 1958–1990, four to 12 REs were used to analyse 74 strains of Ad3 and 76 strains of Ad7. The genome types Ad3a2 and Ad7d predominated for 6 and 11 years, respectively. The genetic relationship between four GTs of Ad3 and eight GTs of Ad7 was investigated further.

MATERIALS AND METHODS

Virus Strains

Of 74 strains of Ad3 isolated during the period 1962–1988, and 76 strains of Ad7 isolated during the period 1958–1990, 43 Ad3 and 54 Ad7 strains were derived from patients with pneumonia. All the patients lived in central and suburban districts of Beijing. We were able to analyse six strains that were retrieved before 1981; all of the other strains were isolated between 1981 and 1990. All strains were isolated in primary human embryo kidney cells and identified as Ad3 and Ad7 by neutralisation tests with rabbit hyperimmune sera against Ad3 and Ad7 at the Departments of Virology, 302nd Hospital and Friendship Hospital, Beijing, China. Virus strains were stored at −20°C. Viral DNA was analysed at the Department of Virology, Umeå University, Sweden.

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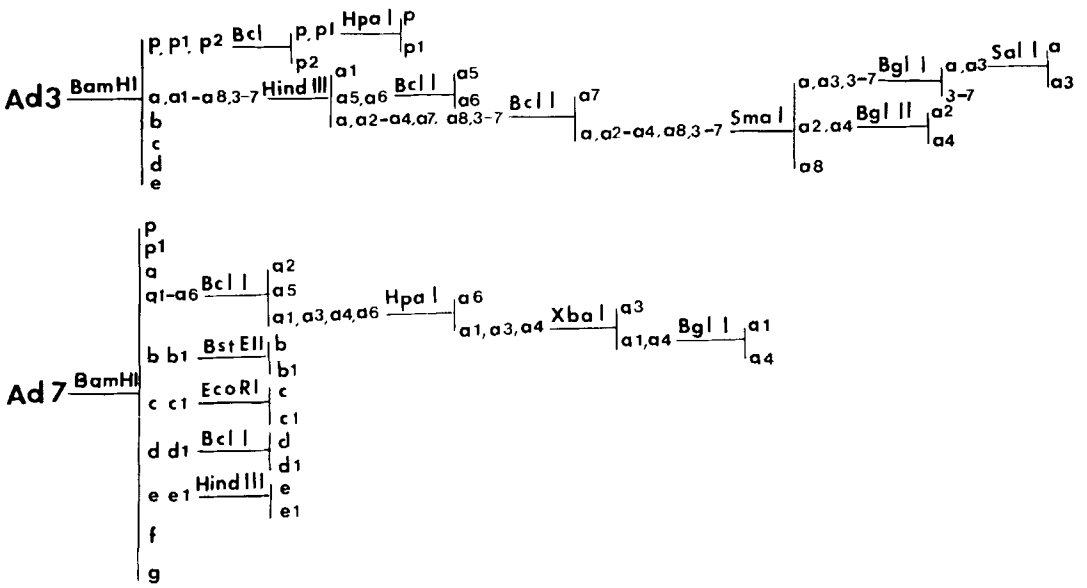

Fig. 1. The pathways for genome type identification of Ad3 and Ad7. These pathways are the most economical and time-saving methods. For instance, all the strains of Ad7 were analysed first with Bam HI. The restriction patterns were compared with known data (Figs. 3–5). Five GTs, 7p, 7p1, 7a, 7f, and 7g, could be directly identified according to their unique patterns. The remaining strains could be allocated to different smaller groups, for example, a1–a6. After the second RE, Bcl I, was used, two other GTs, 7a2 and 7a5, could be identified. The remaining strains could be further analysed with the third RE, Hpa I. Ad7a6 could then be identified. The procedure was continued until the last GT was identified. The nomenclature for GTs was applied according to the protocol described in the Discussion.

In addition to the strains described in the present study, 11 representative strains of Ad7 genome types (7p, 7a, 7a2, 7a3, 7a5, 7a6, 7c, 7c1, 7e, 7e1, and 7f) were used as references [Li and Wadell, 1986]. The two newly identified genome types, Ad7a6 and Ad7e1, were isolated in the United States in 1981 and in Australia in 1975, respectively.

Preparation of Viral DNA

The virus strains were propagated in an A549 cell line. Intracellular viral DNA was extracted with a method described previously [Li et al., 1991].

DNA Restriction Analysis

Based on previous genomic analysis of Ad3 and Ad7 [Li and Wadell 1986, 1988], pathways were designed for genome type identification of Ad3 and Ad7 (Fig. 1) which effectively distinguished all known genome types, using a minimal number of REs. For the analysis of representative strains of each genome type, 12 REs were used (Bam HI, Bcl I, Bgl I, Bgl II, Bst EII, Eco RI, Hind III, Hpa I, Sal I, Sma I, Xba I, and Xho I, purchased from Boehringer Mannheim GmbH and New England Biolabs, Beverly, MA). All enzyme reactions were carried out according to the manufacturers' instructions. Agarose gel electrophoresis of DNA restriction fragments was carried out as described previously [Li et al., 1991].

Nomenclature for Genomic Clusters and Genome Types

The nomenclature published previously [Li and Wadell, 1986] and modified in this communication was applied for genome types and genomic clusters of Ad3 and Ad7.

RESULTS

Identification of Four Genome Types of Ad3

According to the pathway for GT identification of Ad3 (Fig. 1), 74 Ad3 strains were analysed with five REs, Bam HI, Hind III, Bcl I, Sma I, and Bgl II. Four genome types were detected: Ad3a2, Ad3a4, Ad3a5, and Ad4a6 (Table I). These four GTs are closely related genetically as they share 93% to 98% of pairwise comigrating restriction fragments (PCRF). Ad3a2 was first isolated in Beijing in 1962, and predominated from 1983 to 1988. Ad3a4 was the dominant genome type in 1982. Ad3a2 and Ad3a4 are very closely related and share 97% PCRF. Ad3a2 was associated with two fatal cases, and Ad3a4 was associated with one. Ad3a2 isolates accounted for 71.6% of all the carefully analysed strains. Out of the 74 strains, 43 were isolated from patients with pneumonia. Of these 43 strains, 31 were identified as Ad3a2, nine as Ad3a4, and three as Ad3a6.

Identification of Eight Genome Types of Ad7

Seventy-six strains of Ad7 were analysed with four REs, Bam HI, Bcl I, Bgl I, and Bst EII according to the pathway for GT identification of Ad7 (Fig. 1). Over the 33-year observation period (1958–1990), eight different GTs were recognised: Ad7p1, Ad7a1, Ad7a4, Ad7b, Ad7b1, Ad7d, Ad7d1, and Ad7g (Table II). Seven GTs of Ad7 could be distinguished using Bam HI, Bcl I, and Bgl I (Fig. 2), whereas Ad7b1 was distinguished from Ad7b using Bst EII. Ad7d was the predominant GT in

TABLE I. Temporal Distribution of Four Genome Types of Adenovirus Type 3 Isolated in Beijing

Genome type	1962	1981	1982	1983	1984	1985	1986	1987	1988	Total
3a2	$1_{(1^a)}$	1	$2_{(2^a)}$	$17_{(3^a,1^b)}$	$9_{(9^a)}$	$11_{(9^a,2^b)}$	$11_{(11^a)}$	$2_{(2^a)}$	$1_{(1^a)}$	55
3a4			$8_{(6^a,1^b)}$	3			$2_{(2^a)}$			13
3a5				1	1					2
3a6					$2_{(1^a)}$	$2_{(2^a)}$				4
Total	1	1	10	21	12	13	13	2	1	74[c]

[a]The number of strains isolated from patients with pneumonia.
[b]The number of fatal cases.
[c]These 74 strains of Ad3 were isolated from 67 patients, of which 43 were children with pneumonia.

TABLE II. Temporal Distribution of Eight Genome Types of Adenovirus Type 7 Isolated in Beijing

Genome type	1958	1965	1980	1981	1982	1983	1984	1985	1986	1990	Total
7p1				1							1
7a1	$1_{(1^a,1^b)}$										1
7a4	$1_{(1^a,1^b)}$										1
7b	$1_{(1^a,1^b)}$	1									2
7b1				1							1
7d			$17_{(17^a,3^b)}$	$3_{(3^a)}$	$7_{(7^a,1^b)}$	$19_{(14^a,2^b)}$	$7_{(3^a)}$	$4_{(3^a)}$	$2_{(2^a)}$	$8_{(8^a)}$	67
7d1							$2_{(2^a)}$				2
7g	$1_{(1^a,1^b)}$										1
Total	4	1	17	5	7	19	9	4	2	8	76[c]

[a]The number of strains isolated from patients with pneumonia.
[b]The number of fatal cases.
[c]These 76 strains were isolated from 73 patients, of which 54 were children with pneumonia.

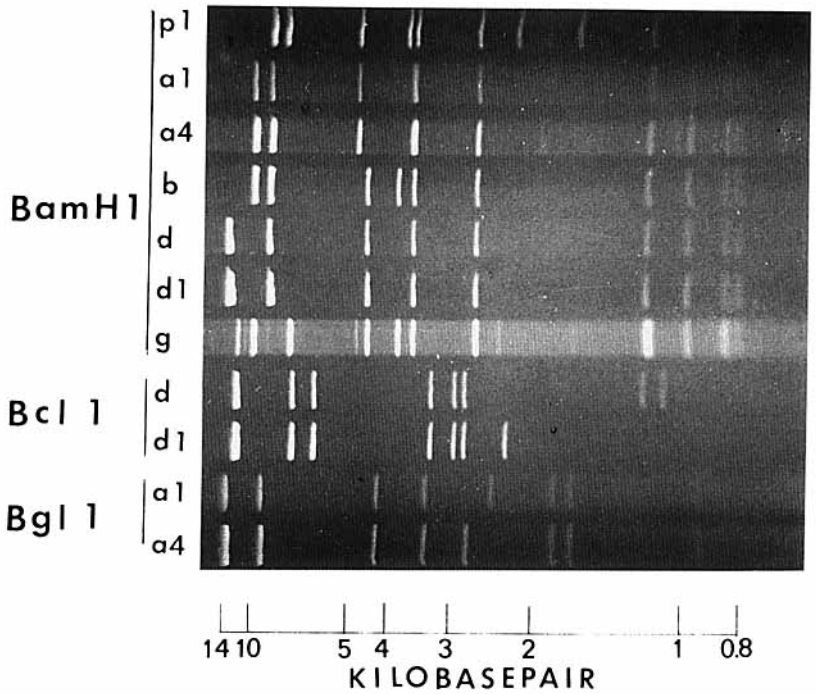

Fig. 2. The seven genome types of Ad7 isolated in China after digestion of the DNA with Bam HI, Bcl I, and Bgl I.

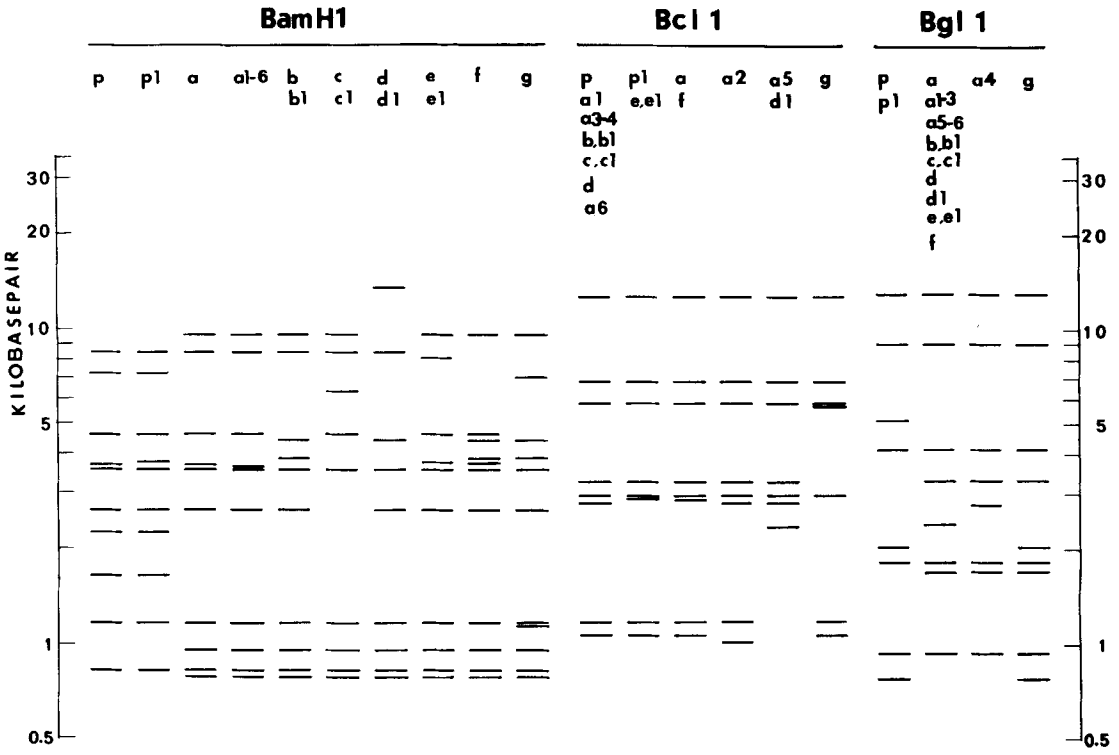

Fig. 3. Schematic presentation of restriction patterns of Ad7 after cleavage of the DNA from 19 genome types with Bam HI, Bcl I, and Bgl I.

Beijing for 11 years (1980–1990), accounting for the majority of the Ad7 isolates (67/76) (Table II). Throughout the observation period, all of the isolates from the central part of the city were identified as Ad7d.

Of the 76 strains, 54 were isolated from patients with pneumonia, 47 of these strains being identified as Ad7d, one Ad7a1, one Ad7a4, two Ad7b, one Ad7g, and two Ad7d1. Neither Ad7b1 nor Ad7p1 occurred in association with pneumonia. One strain of Ad7b1 was isolated from a patient with viral diarrhoea. One strain of Ad7p1 was isolated from an 8-year-old girl with an acute upper respiratory tract infection. Ad7g was isolated from the lung after autopsy of a child who died of infantile pneumonia. Ad7g manifests unique DNA patterns after cleavage with six REs, Bam HI, Bcl I, Bgl I, Bgl II, Bst EII, and Hpa I (Figs. 3–5).

Identification of Three New Genome Types of Ad7

The identification of 15 GTs of Ad7 using 12 REs has been described previously [Li and Wadell, 1986]. Ad7c1 was identified using Eco RI [Kannemeyer et al., 1988]. In this study, three new GTs were found: Ad7b1, Ad7a6, and Ad7e1. Ad7b1 was isolated in Beijing in 1981 from a 7-month-old boy with viral diarrhoea. It has 99% PCRF with Ad7b, and is also related closely to Ad7d (97% PCRF). Ad7a6 was isolated in the United States in 1970. Ad7e1, isolated in Australia in 1975, can be distinguished from Ad7e by Hind III digestion. Ad7e and Ad7e1 are closely related and have 98% PCRF. The restriction patterns of 12 REs allowing identification of these 19 GTs are shown in Figures 3–5.

Same Genome Type in Ten Pairs of Strains

To investigate the possibility of more than one adenovirus genome type occurring in the same patient, ten pairs of adenovirus strains were analysed with 12 REs. Seven pairs were isolated from throat swabs and faeces, two pairs from lungs and throat swabs, and one pair from faeces and urine. The results showed all pairs of isolates to be concordant. Of the ten pairs, Ad3a2, Ad3a4, Ad7d1, and Ad7d were represented by six, one, one, and two pairs, respectively.

Analysis of the Relationship Between Genome Types

Four genome types of Ad3 are very closely related and have 93–98% PCRF. They are grouped in the same genomic cluster (3GC3). The eight GTs of Ad7 could be grouped in three genomic clusters according to the percentage of shared PCRF. Ad7p1 belonged to 7GC1, Ad7g belonged to 7GC2, and the others were grouped in 7GC3.

DISCUSSION

Adenovirus types 3 and 7 are the two of the most important etiological agents of pneumonia in China. Ad3 and Ad7 isolates accounted for 69–100% of Chinese adenovirus strains isolated from patients with pneumonia (Table III). The most serious epidemic of adenovirus-

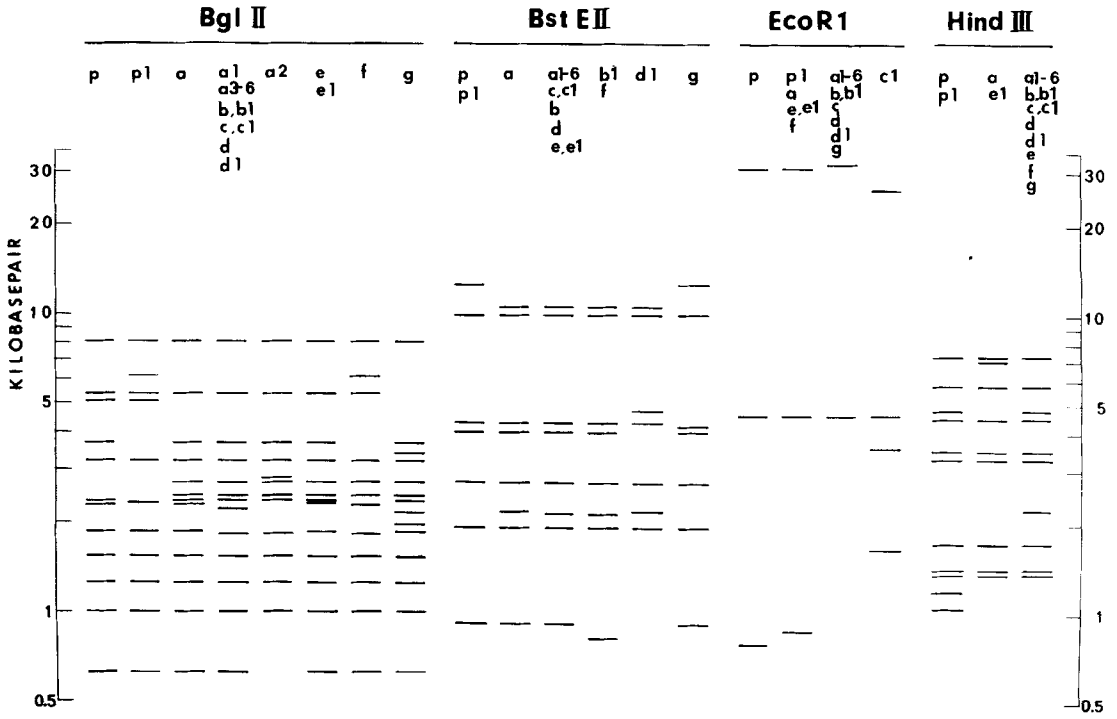

Fig. 4. Schematic presentation of restriction patterns of Ad7 after cleavage of the DNA from 19 genome types with Bgl II, Bst EII, and Hind III.

associated infantile pneumonia ever reported occurred in Beijing, from October 1958 to February 1959. Of 3,398 patients admitted to the Beijing Children's Hospital, 528 died, a fatality rate of 15.5%. In a study of 81 patients, 57 strains of Ad3 and Ad7 were isolated [Teng, 1960]. From the winter of 1960 to the spring of 1964, Ad3 and Ad7 isolates accounted for 73.5% of 548 strains isolated among 790 specimens from children with pneumonia. The fatality rate in infantile pneumonia caused by Ad3 and Ad7 was 12.6% and 24%, respectively. Thus Ad7 is the more virulent of the two [Wang et al., 1965].

The present data show Ad3 and Ad7 to have been the main adenovirus serotypes causing pneumonia (Table III). In a long-term survey of adenoviral pneumonia (1958–1990), Ad7 was associated with a higher fatality rate (10/54) than Ad3 (4/43). However, clinicians have observed that the symptoms manifested during infection with Ad3 and Ad7 have become less severe since the mid-1980s. No fatal case has occurred since 1986, and no strain of Ad7 was isolated during the period 1987–1989. This may have been due to a lack of change in the predominant genome types of Ad3 and Ad7, enabling community-specific antiadenoviral immunity to remain at a higher level in the Beijing population, providing a widespread maternal immunity to Ad3 and Ad7.

A study of molecular epidemiology of adenoviruses, undertaken at the Department of Paediatrics, Bethune University of Medical Sciences in Northern China, revealed the occurrence of three GTs of Ad3 and two GTs of Ad7 after cleavage of the DNA of 46 Ad3 and 56 Ad7 isolates with two and six REs, respectively. Ad7b predominated from 1976 to 1985, but has not been isolated since 1985. Ad7d was found in 1982 and predominated after 1985 [Fu et al., 1989]. Although Ad7b has spread throughout the world [Wadell et al., 1985], it has not been isolated in Beijing since 1965, possibly owing to inefficient surveillance. Ad7d was first isolated in 1980. The shift from Ad7b to Ad7d may have occurred between 1965 and 1980, at least 2 years earlier than observed in Changchun, 1982–1985 [Fu et al., 1989].

During epidemics, several genome types of the same serotype frequently cocirculate. For instance, during the epidemic of viral pneumonia in the winter of 1958, four GTs of Ad7 were isolated from lung specimens obtained at autopsy. These four GTs belong to two genomic clusters: 7GC2 (Ad7g) and 7GC3 (Ad7a1, Ad7a4, and Ad7b). Ad7a1 and Ad7a4 are very closely related and share 99% PCRF. There may have been genetic drift from one genome type to the other. Ad7g is distinctly different from other GTs and has 81% PCRF and 72% PCRF with Ad7b of 7GC3 and with Ad7p1 of 7GC1, respectively.

During an outbreak of Ad3 infections in Beijing in August 1983, three GTs, Ad3a2, Ad3a4, and Ad3a5, were isolated in 1 month. Ad3a2 predominated in Beijing for 26 years (1962–1988) except during 1982 when Ad3a4 was the most prevalent GT. Ad3a2 was found to be closely related to Ad3a4 and Ad3a5 sharing 97% PCRF. Ad3a4 and Ad3a5 share 93% PCRF. Thus, Ad3a4 and Ad3a5 may be the result of genetic drift from Ad3a2.

On the basis of these observations, it is concluded that cocirculation of several genome types may occur during the same period, mirroring genetic drift and shift.

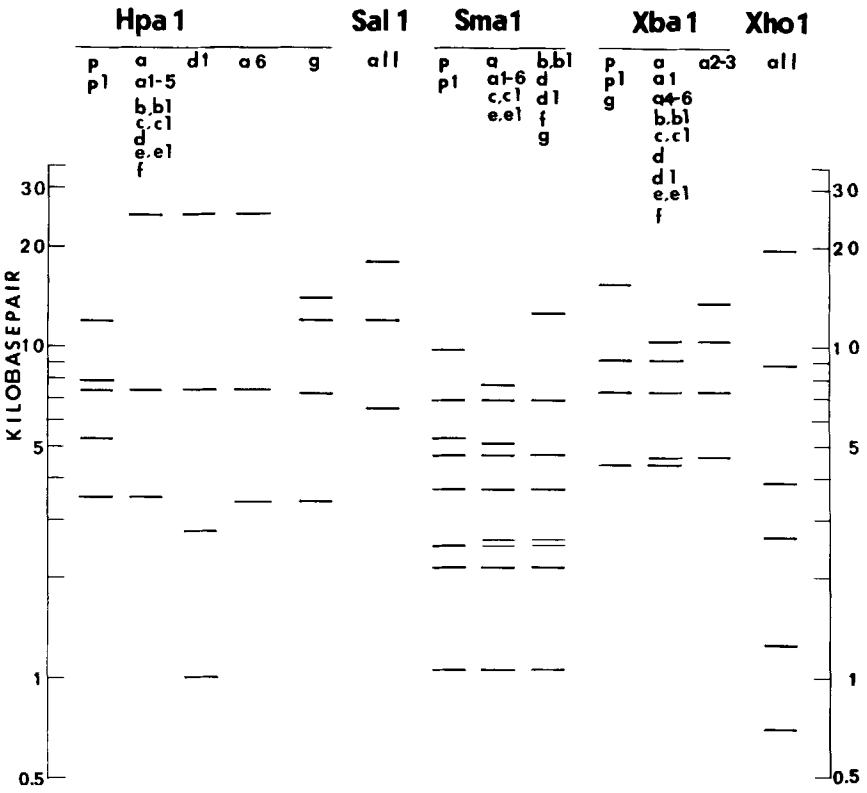

Fig. 5. Schematic presentation of restriction patterns of Ad7 after cleavage of the DNA from 19 genome types with Hpa I, Sal I, Sma I, Xba I, and Xho I. Four restriction DNA fragments of Ad7a6 (25,000, 7,400, 3,400, and 100 bp in size) were found after cleavage with Hpa I. The smallest fragment of 100 base pairs is not shown.

TABLE III. Adenovirus Strains Isolated From Patients With Pneumonia in China

Period	Place	Number of strains			References
		Total	Ad3	Ad7	
1958–81	Changchen (Northern China)	733	368	295	Fu et al. [1985]
1973–83	Guangzhou (Southern China)	225	90	94	Chang et al. [1985]
1958–59	Beijing	57	57[a]		Teng [1960]
1973–75	Beijing	74	19	52	Chiu et al. [1977]
1959–60	Beijing	16	5	9	Dai et al. [1962]
1960–64	Beijing	548	184	219	Wang et al. [1965]
1981–83	Beijing	41	14	16	Zhang et al. [1985]
1962–88	Beijing	160[b]	60	50	This report

[a]The 57 strains of Ad3 and Ad7 isolated from 81 children with pneumonia, but no numerical data were reported for individual serotypes.
[b]Of the 160 strains, Ad1, Ad2, and Ad5 were represented by 21, 16, and 12 strains, respectively, and Ad11 by one strain.

Genomic analysis with REs has become a useful tool in molecular epidemiology. The technique, now widely used for studies of adenoviruses [Wigand and Adrian, 1991], not only provides an additional dimension to the analysis of the distribution of adenoviruses, but also allows determination of the circulation and relationship of specific variants or genome types isolated from different areas at different times.

A single base change at a restriction site of the viral DNA can be observed as an altered restriction enzyme fragment pattern in an agarose gel. Numerous genome types have been and will continue to be discovered. As the REs and nomenclature systems used differ between laboratories [Adrian et al., 1985; Li and Wadell 1986; Golovina et al., 1991; Itakura et al., 1990], a rational system is required for the classification and nomenclature of genome types.

A nomenclature system has been suggested [Li and

Wadell, 1986] and applied for the description of many genome types at different laboratories [Arens and Worth, 1988; Fu et al., 1989; Guo et al., 1988; Kannemeyer et al., 1988; Golovina et al., 1991]. We now describe it in detail with a minor modification. Briefly, new genome types are designated according to the following protocol:

A. Restriction endonucleases recognising hexanucleotides are used. They should preferentially be inexpensive and widely available.
B. Initially, numerous adenovirus strains from different continents selected over several decades should be screened using several REs. Among these, the restriction endonuclease that can recognise the largest number of genome types is selected as the discriminating enzyme. For instance, Bam HI was selected as the discriminating enzyme for Ad7, because ten restriction patterns had been identified after analysis of 51 strains isolated from five continents. The genome types were designated "P" for prototype, "a" for the genome types subsequent to the prototype, as already described by Rowe and co-workers [Rowe et al., 1958], then b, c, etc., in chronological order of identification.
C. The Arabic numeral after p, a, b, etc., denotes the different genome types distinguished by means of additional REs. The Arabic numerals were added in chronological order of identification of the genome types.
D. The results of analysis of PCRF for genome types revealed the occurrence of genomic clusters (GCs). A statistically significant difference should be demonstrated between the mean PCRF identity within a GC and that between two GCs [Li and Wadell, 1988]. The GC containing the prototype of an adenovirus serotype was named GC1. GCs including distinctly different strains isolated subsequent to the prototype are designated in chronological order of identification as GC2, GC3, etc.

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